#AHA24

Nexiguran Ziclumeran (nex-z, Also Known as NTLA-2001), an Investigational *In Vivo* CRISPR-Based Therapy for Patients With Transthyretin Amyloidosis With Cardiomyopathy (ATTR-CM): Interim Report of the Phase 1 Study

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Disclosures

- Dr. Fontana reports consultancy/advisory boards for Alexion/Caelum Biosciences, Alnylam Pharmaceuticals, AstraZeneca, Attralus, BridgeBio/Eidos, Cardior Pharmaceuticals, Intellia Therapeutics, Ionis Pharmaceuticals, Janssen Pharmaceuticals, Lexeo Therapeutics, Novo Nordisk, Pfizer, and Prothena
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ATTR Amyloidosis Is a Progressive and Fatal Disease

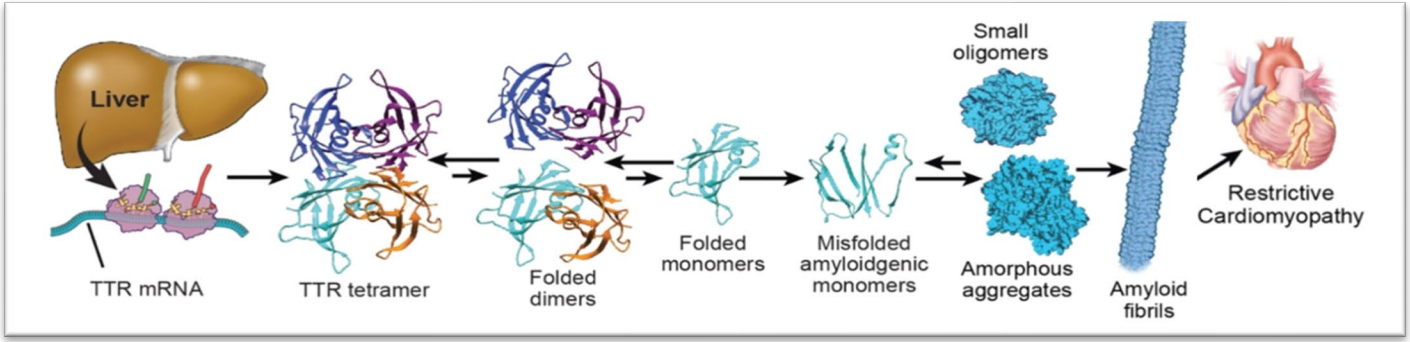


Figure modified from Ruberg FL, et al. *J Am Coll Cardiol* 2019;73:2872-2891.

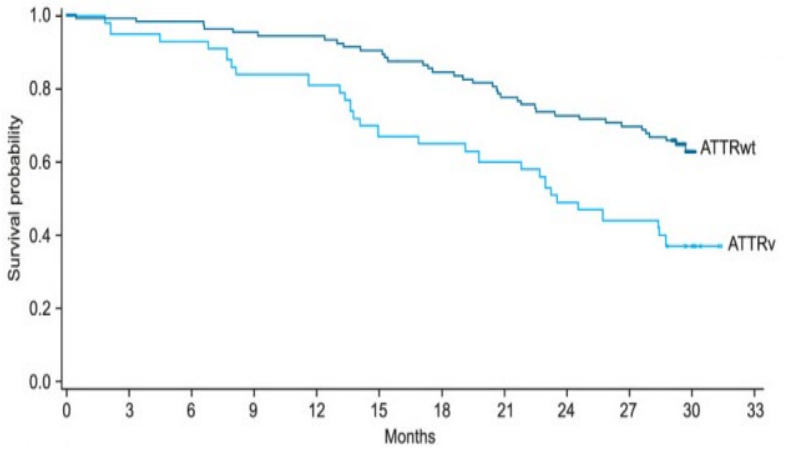
- Transthyretin amyloidosis with cardiomyopathy (ATTR-CM) results from accumulation of wild type or variant TTR amyloid fibrils in the heart, and is a progressive and fatal disease[1]
- ATTR-CM is an often underdiagnosed cause of heart failure, and is estimated to impact 200,000-500,000 patients globally[2-4]
- Currently available treatments for ATTR-CM include TTR stabilizers and *TTR* gene silencers; however, quality of life and functional capacity continue to decline, and they require lifelong administration

mRNA, messenger RNA; TTR, transthyretin.

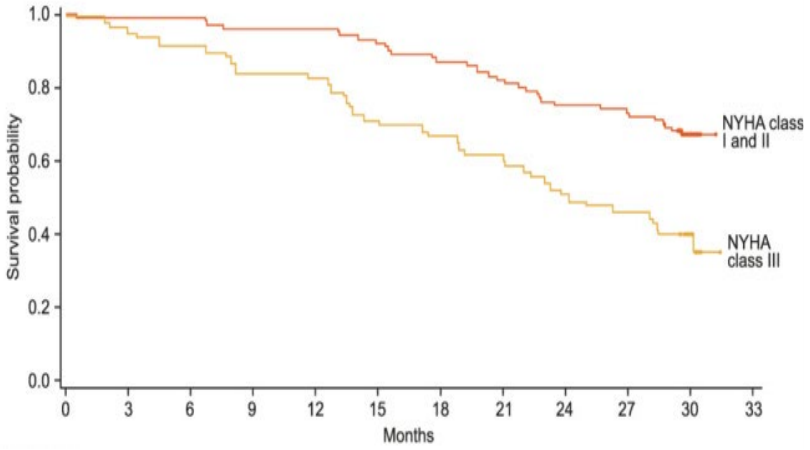
1. Ruberg FL, et al. *J Am Coll Cardiol* 2019;73(22):2872-2891. 2. Maurer M, et al. *Circ Heart Fail.* 2019;12(9):e006075. 3. Nativi-Nicolau JN, et al. *Heart Fail Rev.* 2021;27(3):785-793. 4. Gillmore JD, et al. Presented at: American Heart Association® Scientific Sessions; Chicago, IL; November 5, 2022.

Probability of Survival in Patients With Either Hereditary Disease (ATTRv) or NYHA Class III

All-Cause Mortality by Genotype[1]
ATTR-ACT patients receiving placebo



All-Cause Mortality by NYHA Class at Baseline[1]
ATTR-ACT patients receiving placebo

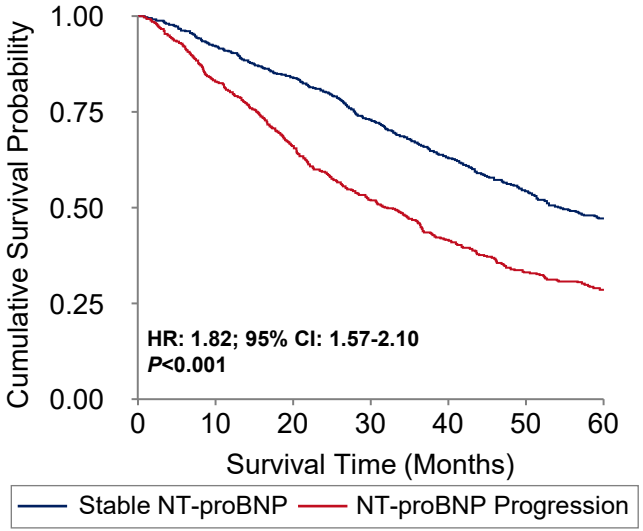


Mortality rates are higher in patients with hereditary disease or those with NYHA class III[1]

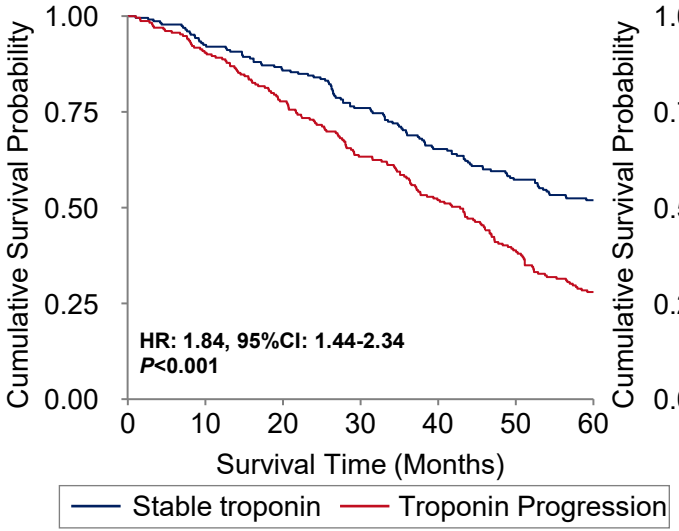
[a]All patients in this analysis were receiving treatment with placebo.
ATTRv, hereditary/variant ATTR amyloidosis; ATTRwt, wild-type ATTR amyloidosis; NYHA, New York Heart Association.
1. Nicolau JN, et al. *ESC Heart Fail*. 2021;8(5):3875-3884.

Worsening of NT-proBNP, Troponin T, and 6MWT Is Associated With an Even Greater Risk of Death in Patients With ATTR-CM

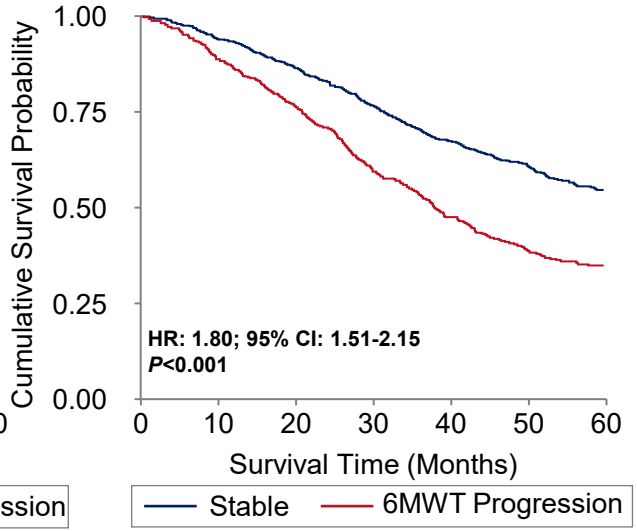
Survival according to NT-proBNP progression[1]
Increase of >700 ng/L and >30%



Survival according to troponin progression[1]
Increase of >10 ng/L and >20%



Survival according to 6MWT progression[2]
Reduction of >35 m



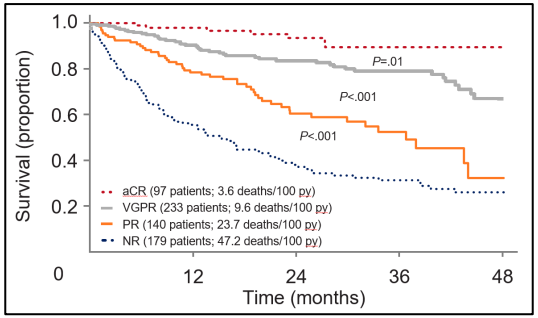
In patients with ATTR-CM (≈80% NYHA class I/II)[1], worsening of NT-proBNP, troponin T, and 6MWT occurred at 12 months in 35%, 50% and 40%, respectively

6MWT, 6-Minute Walk Test; ATTR-CM, ATTR amyloidosis with cardiomyopathy; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
1. Ioannou A, et al. *J Am Coll Cardiol*. 2024;83(14):1276-1291. 2. Ioannou A, et al. *J Am Coll Cardiol*. 2024;84(1):43-58.

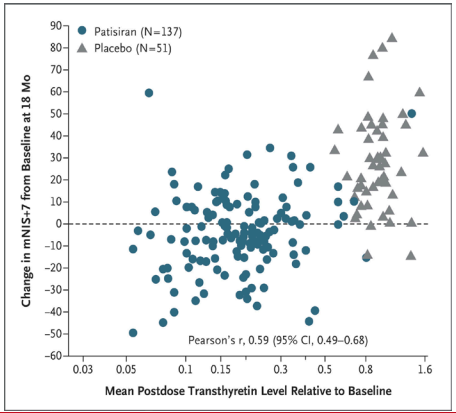
TTR Lowering Has Proven to Lead to Improved Clinical Outcomes in ATTR Amyloidosis

- In patients with ATTR-CM, vutrisiran, a *TTR* gene silencer, led to a lower risk of death and CV events[1]
  - Mean TTR reductions of ≈80% reached at 6 months
  - Mean (SD) absolute TTR levels were 50 (46) µg/mL
- Achieving the lowest possible level of amyloid precursor protein is likely to be important to maximally impact disease progression in ATTR-CM
  - Greater suppression in the amyloid precursor protein, in amyloid A protein (AA) and immunoglobulin light chain amyloidosis, is associated with better outcomes[2-4]
  - Deeper reductions in TTR levels have been correlated with increased clinical benefit in patients with ATTRv-PN[5]

Survival Based on Hematologic Response in AL Amyloidosis[4]



Correlation of Reduction in TTR Levels With Change in mNIS+7 From Baseline to 18 Months[5]

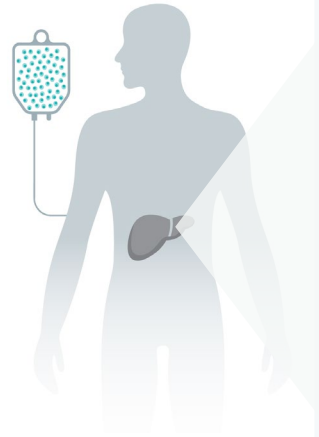


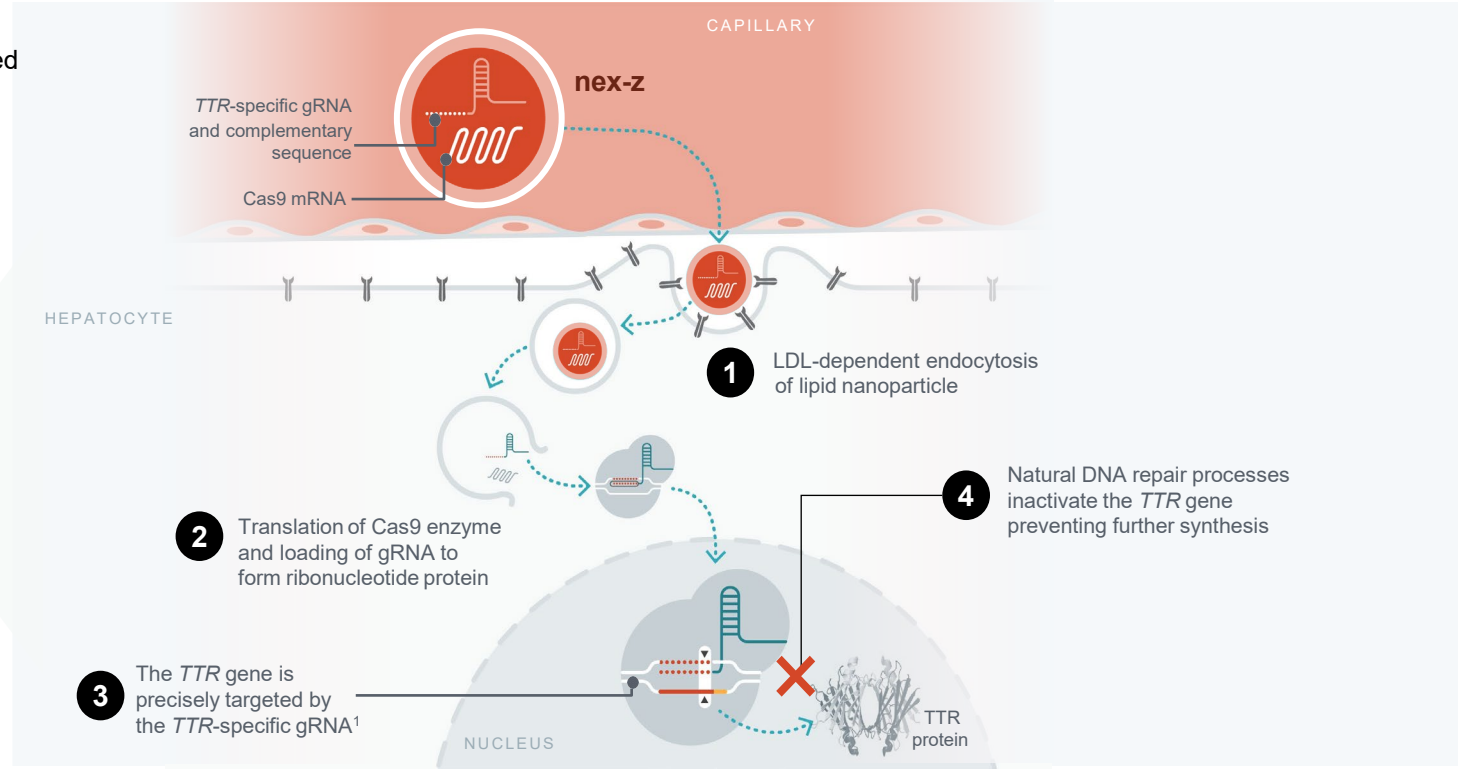
aCR, amyloid complete response; AL, immunoglobulin light chain; CM, cardiomyopathy; CV, cardiovascular; mNIS, modified Neuropathy Impairment Score; NR, no response; PR, partial response; PN, polyneuropathy; TTR, transthyretin; VGPR, very good partial response.

1. Fontana M, et al. *N Engl J Med*. 2024; DOI: 10.1056/NEJMoa2409134. 2. Gillmore JD, et al. *Lancet*. 2001;358(9275):24-29. 3. Lachmann HJ, et al. *Br J Haematol*. 2003;122(1):78-84. 4. Palladini G, et al. *J Clin Oncol*. 2012;30(36):4541-4549. 5. Adams D, et al. *N Engl J Med*. 2018;379(1):11-21.

Nex-z, an *In Vivo* Investigational CRISPR/Cas9 Therapy, Inactivates the *TTR* Gene, Whether Wild-Type or Variant, With a One-Time Treatment[1]

A one-time IV infusion delivered over 4 hours is used to administer nex-z, a CRISPR/Cas9 gene editing therapy[2]





CRISPR/Cas9, clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9; gRNA, guide RNA; IV, intravenous; LDL, low density lipoprotein; mRNA, messenger RNA; TTR, transthyretin.

1. Gillmore JD, et al. *N Engl J Med.* 2021;385(6):493-502. 2. Intellia Therapeutics. Data on file.

Two-Part, Open-Label Study in Adults With ATTR-CM

Hereditary transthyretin amyloidosis with cardiomyopathy (ATTRv-CM) or wild-type cardiomyopathy (ATTRwt-CM), NYHA Class I-III

Intervention:
Single dose administered via an IV infusion

PART I – DOSING COMPLETE
Single-Ascending Dose

- 1.0 mg/kg NYHA Class I/II (n=3)
- 0.7 mg/kg NYHA Class I-III (n=9)

PART II
Dose Expansion

- 55 mg NYHA Class I-III (n=24)

PRIMARY OBJECTIVES

Evaluate safety, tolerability, and PD

- *Measure serum TTR levels*

SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of cardiac disease

- *Biomarkers of disease progression including NT-proBNP, hs-Troponin T, and 6MWT, cardiopulmonary exercise test, cardiac imaging, and KCCQ score*

Clinicaltrials.gov ID: NCT04601051

[a]NYHA class I-III and NT-proBNP >600 pg/mL (or, if patient has known diagnosis of atrial fibrillation, NT-proBNP >1000 pg/mL).
[b]Patients with non-ATTR amyloidosis or known leptomeningeal ATTR amyloidosis were excluded.
6MWT, 6-Minute Walk Test; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PD, pharmacodynamics; TTR, transthyretin.

Demographics and Baseline Characteristics

Characteristic	All patients (N=36)
Age, median (min, max), y	78.0 (46, 90)
Sex, male, n (%)	35 (97)
Black or African descent	8 (22)
White or Caucasian	28 (78)
NT-proBNP, median (min, max), ng/L	2052 (851, 19624)
hs-Troponin T, median (min, max), ng/L	56 (15, 204)
eGFR, median (min, max), mL/min/1.73 m^2	65.1 (32.7, 96.3)
6-Minute Walk Test distance, median (min, max), m	331 (178, 580)
Peak VO_2, median (min, max), mL/kg/min	12.7 (7.8, 28.4)
CMR extracellular volume, median (min, max), %	58 (45, 71)

Characteristic	All patients (N=36)
TTR genotype, n (%)	
Wild type	25 (69)
p.V142I[a]	7 (19)
Other mutations	4 (11)
NYHA class, n (%)	
I	3 (8)
II	15 (42)
III	18 (50)
Tafamidis use at baseline, n (%)	0 (0)

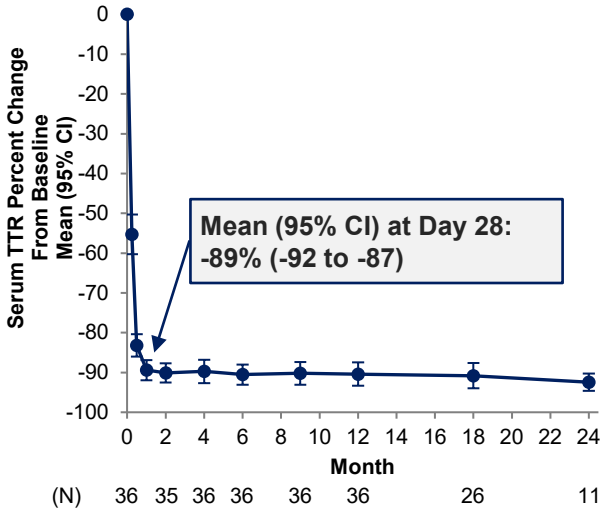
Population representative of ATTR-CM, including patients with advanced disease

Data cutoff August 21, 2024. Percentages may not total 100 because of rounding.
[a]Includes 2 homozygous patients.
ATTR-CM, ATTR amyloidosis with cardiomyopathy; CMR, cardiac magnetic resonance imaging; eGFR, estimated glomerular filtration rate; hs, high sensitivity; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TTR, transthyretin; VO_2, oxygen consumption.

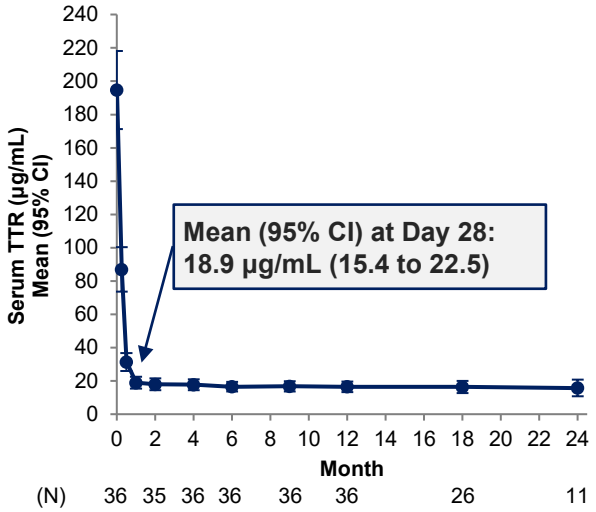
Nex-z Led to Deep, Rapid, and Durable Reductions in Absolute Serum TTR in Every Patient Following a Single Dose

Change in Serum TTR Levels Through Month 24

Percent Change From Baseline



Absolute Serum TTR



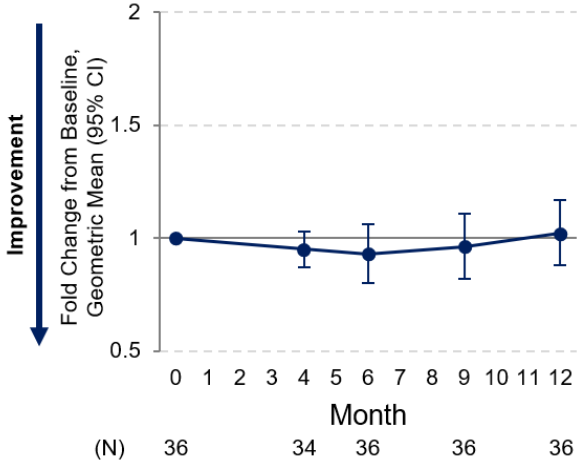
Similar serum TTR reductions were observed in every patient, regardless of baseline TTR level or genotype.
Mean absolute serum levels of 18.9 µg/mL achieved at Day 28, with levels remaining virtually unchanged through 24 months.

Data cutoff August 21, 2024.
TTR, transthyretin.

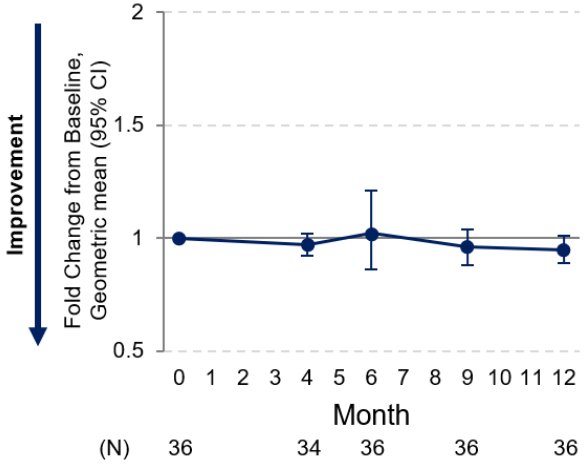
Nex-z Treatment Led to Stability of NT-proBNP, hs-Troponin T, and 6MWT Over 12 Months

Markers of Disease Progression[1]

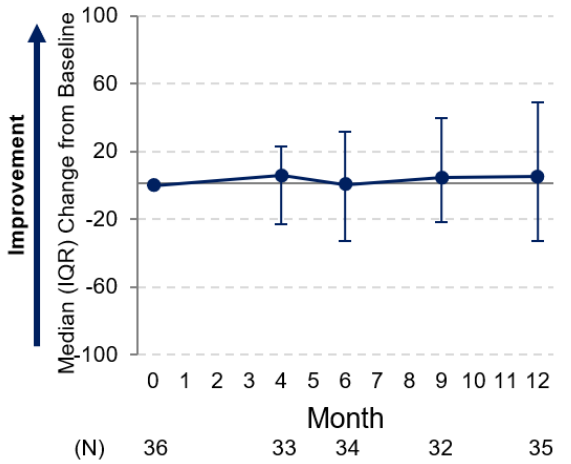
NT-proBNP



hs-Troponin T

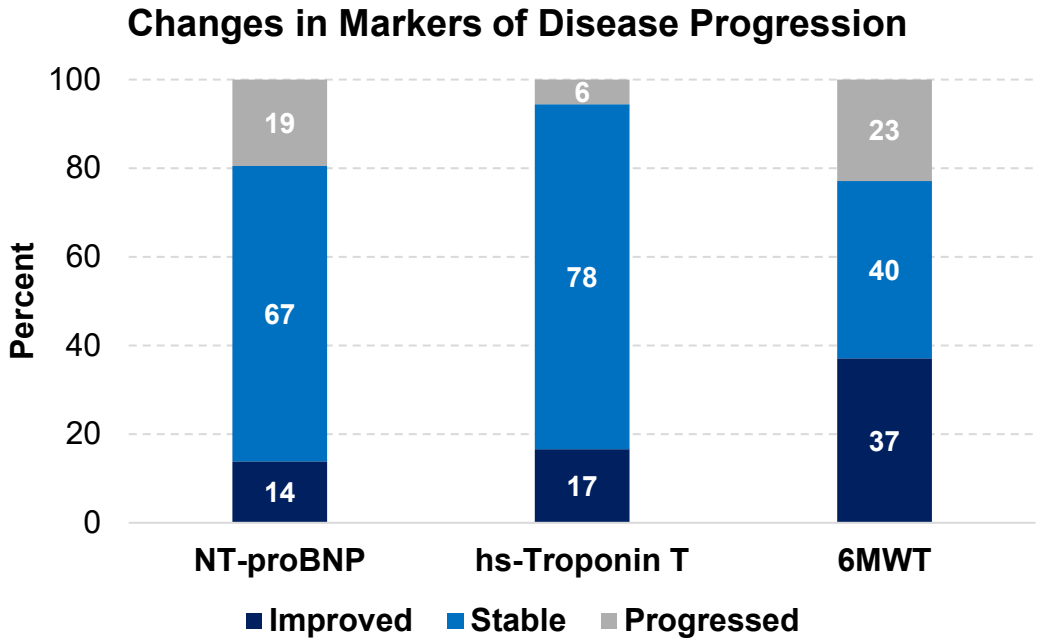


6MWT Distance (meters)



Data cutoff August 21, 2024.
6MWT, 6-Minute Walk Test; hs, high sensitivity; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
1. Ioannou A. et al. *J Am Coll Cardiol*. 2024;83(14):1276-1291.

Nearly 80% of Patients Demonstrated Stability or Improvement in Markers of Disease Progression



Disease Progression Criteria[1,2]:

- NT-proBNP: an increase of >700 ng/L and >30%
- hs-Troponin T: an increase of >10 ng/mL and >20%
- 6MWT: an absolute reduction of >35 m in 6MWT distance

Improvement was defined as the equivalent counter criteria

83% of NYHA class I/II patients and 47% of NYHA class III patients had no worsening in any marker at 12 months

Data cutoff August 21, 2024. Percentages may not total 100 because of rounding.
6MWT, 6-Minute Walk Test; hs, high sensitivity; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
1. Ioannou A. et al. *J Am Coll Cardiol*. 2024;83(14):1276-1291. 2. Ioannou A. et al. *J Am Coll Cardiol*. 2024;84(1):43-58.

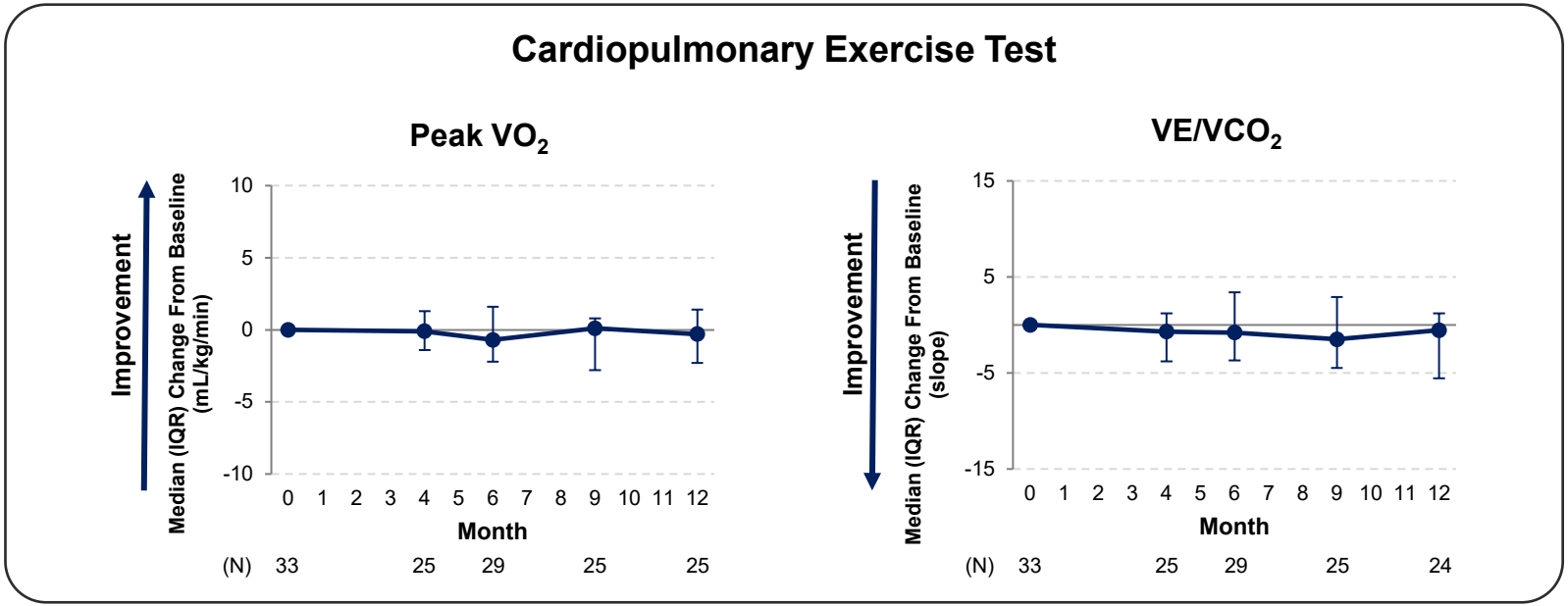
Evidence of Stability or Improvement in Symptoms and QOL in Most Patients Following nex-z Treatment

Endpoint	Overall (N=36)	NYHA Class I/II (n=18)	NYHA Class III (n=18)
KCCQ Overall Score at Month 12			
Median change (IQR)	7.8 (-0.5, 15.4)	5.2 (-3.6, 10.9)	9.0 (0.8, 18.8)
Change in NYHA Class at Month 12[a]			
Improved, n (%)	17 (47)	4 (22)	13 (72)
No change, n (%)	16 (44)	11 (61)	5 (28)
Worsened, n (%)	3 (8)	3 (17)	0 (0)

92% of patients demonstrated either no change or improvement in NYHA class at 12 months, including improvement in 72% of patients with NYHA class III

[a]Values represent a change of at least one level in NYHA class.
IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; QOL, quality of life.

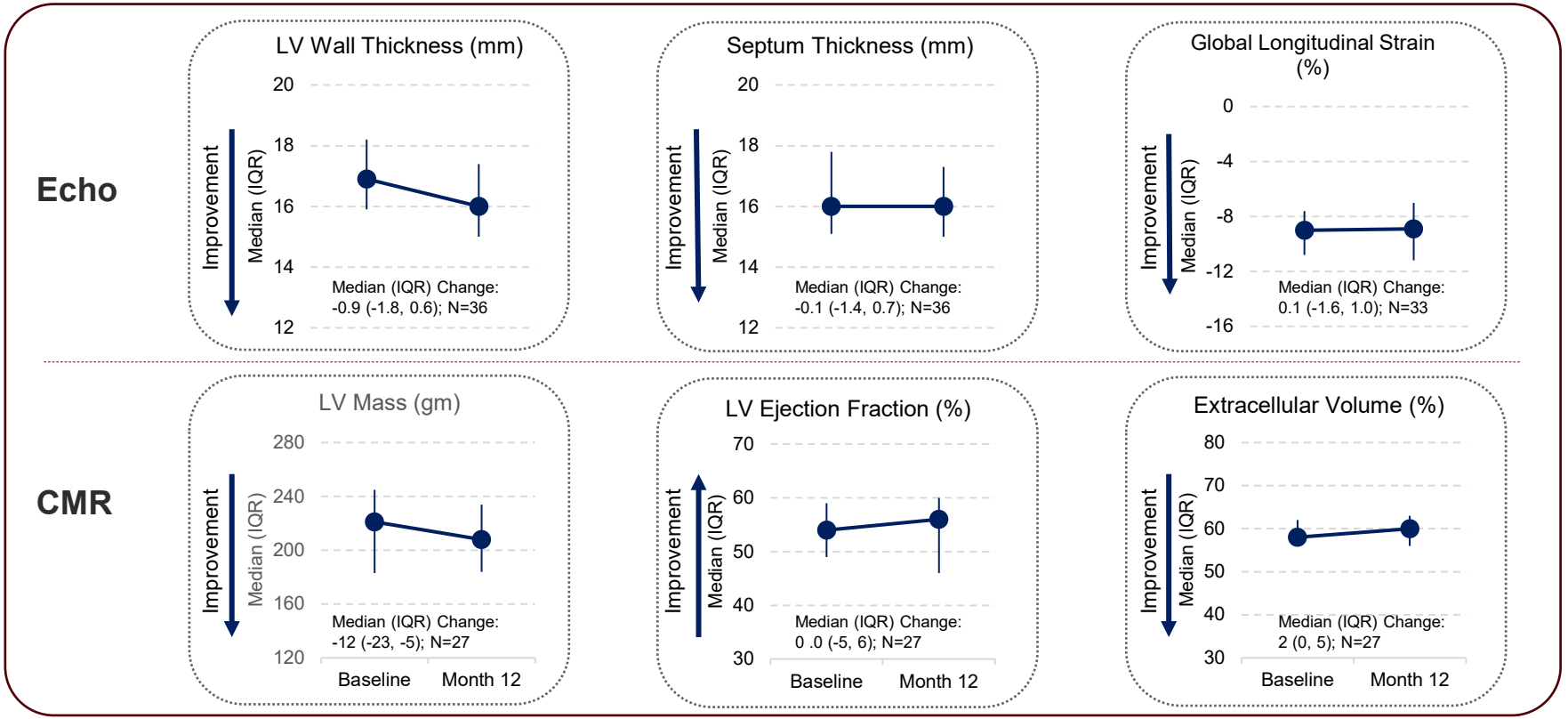
Functional Capacity Remained Stable Through 12 Months Following nex-z Treatment



Peak VO_2 and VE/VCO_2 slope are strong prognostic markers[1] and deteriorate rapidly in ATTR-CM[2]

Data cutoff August 21, 2024.
ATTR-CM, ATTR amyloidosis with cardiomyopathy; IQR, interquartile range; VE/VCO_2, ventilatory efficiency; VO_2, oxygen consumption.
1. Patel RK, et al. *JAMA Cardiol*. 2024;9(4):367-376. 2. Argirò A, et al. *Can J Cardiol*. 2024;40(3):364-369.

Imaging Assessments of Cardiac Remodeling Showed a Similar Pattern of Stability Following nex-z Treatment



Data cutoff August 21, 2024.
CMR, cardiac magnetic resonance imaging; IQR, interquartile range; LV, left ventricular.

Summary of Safety

Event	n (%)
At least one AE	34 (94)
AEs occurring in ≥15% of patients	
Cardiac failure	13 (36)
COVID-19	7 (19)
Upper respiratory tract infection	7 (19)
Atrial fibrillation	6 (17)
Urinary tract infection	6 (17)
Treatment-related AEs in ≥5% of patients	
Infusion-related reaction	5 (14)
Aspartate aminotransferase increased	2 (6)
Any AE leading to treatment discontinuation	0
Any event leading to death[a]	1 (3)

Event	n (%)
Any SAE	14 (39)
SAEs occurring in ≥5% of patients	
Cardiac failure	5 (14)
Acute myocardial infarction	3 (8)
Urinary tract infection	3 (8)
Atrial flutter	2 (6)
Pneumonia	2 (6)
SAEs of heart failure or arrhythmia	7 (19)
Cardiac failure	5 (14)
Arrhythmia[b]	3 (8)
CV hospitalization rate[c] (n/pt/yr, 95% CI)	0.16 (0.08 to 0.36)

Data cutoff August 21, 2024. Median (min, max) follow-up for safety was 18 months (12, 27). For each preferred term, subjects reporting more than one adverse event are counted only once.
Liver enzyme elevations were transient, generally mild, and not indicative of liver injury. [a]Only one death occurred (ischemic heart disease) on Day 506 after dosing; unrelated to treatment.
[b]Arrhythmia events included SAEs of atrial flutter and atrioventricular block complete, with one patient experiencing both cardiac failure and arrhythmia on the same day. [c]Includes hospitalizations for cardiac failure, arrhythmia, or stroke.
AE, adverse event; CV, cardiovascular; SAE, serious AE.

Summary

- A single dose of nex-z demonstrated favorable safety and tolerability and resulted in deep, rapid, and durable reductions in serum TTR with very low variability among all patients in the study

- Reductions in TTR were accompanied by stability or improvement of several disease markers in an ATTR-CM population with advanced disease who are expected to have rapid disease progression and high mortality rates

- The effects of nex-z observed in this ongoing phase 1, single arm, open-label study will need to be confirmed in randomized controlled trials

ATTR-CM, ATTR amyloidosis with cardiomyopathy; TTR, transthyretin.

Conclusions

- These results represent the first clinical evidence of *in vivo* CRISPR/Cas9 gene editing in cardiomyopathy showing that targeted inactivation of the *TTR* gene may favorably impact disease progression in ATTR-CM

- These results also support the hypothesis that rapid, deep, and durable reductions in serum TTR result in meaningful clinical benefits

- The effects of nex-z on clinical outcomes are being evaluated in MAGNITUDE[a], a phase 3, global, randomized, placebo-controlled trial in patients with ATTR-CM

[a]NCT06128629.
ATTR-CM, ATTR amyloidosis with cardiomyopathy; CRISPR/Cas9, clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9; TTR, transthyretin.

Acknowledgments

- We wish to extend our gratitude to the patients, their caregivers, and their families, study site coordinators, and staff

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ORIGINAL ARTICLE

CRISPR-Cas9 Gene Editing with Nexiguran Ziclumeran for ATTR Cardiomyopathy

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THANK YOU

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